Remarks

The Amendments to Claim 1

Claim 1 has been amended to recite a method of "desensitizing an individual to an allergen" comprising the step of delivering an allergen "against which the individual mounts an allergic response" directly into a lymph node of said individual, whereby the "individual is desensitized to the allergen." This amendment is supported at page 10, lines 17-23: "The present invention involves the delivery of an allergen by injection directly into a lymph node in order to modulate an allergic response of an individual . . . [M]odulation of an allergic response includes, but is not limited to, . . . lowered sensitivity to the allergen . . . ." The amendment does not add new matter and does not require a new search.

Objection to the Drawings

Corrected drawings accompany this amendment.

Objection to the Declaration

The Office Action requires a new declaration because Dr. McCormack made "[n]on-initialed and/or non-dated alterations" to the original declaration. The Office Action points to M.P.E.P. § 602.01 and 37 C.F.R. § 1.52(c) as supporting the objection. Applicants' representative has reviewed the cited sections and finds no support for requiring a new declaration.

Section 1.52(c) of 37 C.F.R. states that "[a]ny interlineations, erasure, cancellation or other alteration ***of the application papers filed*** must be made before the signing of any

accompanying oath or declaration pursuant to § 1.63 referring to those application papers and should be dated and initialed or signed by the applicant ***on the same sheet of paper***." (emphasis added). Dr. McCormack did not interlineate, erase, cancel or make any other alteration of any of the application papers filed. He merely corrected a typographical error in the name of his city of residence.

M.P.E.P. § 602.01 states that "The wording of an oath or declaration cannot be amended, altered or changed in any manner after it has been signed." Dr. McCormack did not change the wording of the declaration. The M.P.E.P. also states that "in some cases, a deficiency in the oath or declaration can be corrected by a supplemental paper such as an application data sheet . . . ***and a new oath or declaration is not necessary.*** See 37 C.F.R. § 1.63(c)(1) and (c)(2)." M.P.E.P. § 602.01, emphasis added. Section 1.63(c)(1) of 37 C.F.R. is the section referring to identification of the inventor's mailing address and residence.

In compliance with M.P.E.P. § 602.01 and 37 C.F.R. § 1.63(c)(1), an application data sheet, correcting Dr. McCormack's city of residence, accompanies this amendment.

Objection to the Specification

The specification is objected to for not providing proper antecedent basis for the recitation of "0.01 μg" in original claim 23. The specification has been amended to provide the proper antecedent basis.

The Rejection of Claims 1-10, 14, 19-26, 45, and 46 Under 35 U.S.C. § 112, first paragraph

Claims 1-10, 14, 19-26, 45, and 46 stand rejected under 35 U.S.C. § 112, first paragraph, both as not enabled for their full scope and as lacking sufficient written description in the specification. Applicants respectfully traverse both rejections.

Enablement

Claims 1-10, 14, 19-26, 45, and 46 are directed to methods of desensitizing an individual to an allergen. The claimed methods involve intranodal delivery of an allergen against which the individual mounts an allergic response. The individual is thereby desensitized to the allergen. The Office Action acknowledges that the claimed methods are enabled for methods of intranodal injection of phospholipase A2 to modulate an increase in antigen-specific IgG2a and a decrease in antigen-specific IgE. The Office Action asserts, however, that the specification does not enable intranodal injection of any allergen to modulate any allergic response. Page 3, paragraph no. 9.

The legal test for whether a disclosure provides adequate enablement for a generic claim is that "the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). The law is clear that the specification need not provide knowledge that is generally known by those skilled in the art. Applicants can properly rely on common knowledge in the art to bolster and supplement the teachings of the specification. *Genentech Inc. v. Novo Nordisk A/S*, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). The present specification, therefore, need only "supply the novel aspects of [the] invention in order to constitute adequate enablement." 42 U.S.P.Q.2d (BNA) at 1005.

The novel aspect of the invention is the *intranodal* injection of an allergen to desensitize an individual to the allergen. The specification teaches that intranodal delivery of an allergen more efficiently modulates an allergic response than is possible by subcutaneous injection. Page 10, lines 17-20. In addition, the specification teaches that

> Intranodal administration of allergens has a number of advantages. Because lower doses of allergen can induce an IgG response more potently when injected directly into a lymph node, there are fewer side effects than observed using the conventional allergy shot regime. Moreover, delivery of the allergen to the lymph node by injection is no more painful to the patient than regular subcutaneous injections. An additional advantage of this method is that only two or three treatments typically are necessary to desensitize an individual against an allergen. This lowers the risk of side effects or reaction to the administration, and results in a significant cost savings compared with traditional allergy treatments.

Page 11, lines 3-11. The specification provides numerous examples of the types of allergic responses that can be modulated:

> According to the invention, modulation of an allergic response includes, but is not limited to, diminution or elimination of responses such as alterations in specific IgG levels, alterations in IgG ratios, alterations in specific IgE levels, lowered sensitivity to the allergen or to a cross-reactive allergenic agent, alterations in activated basophils (such as the reduction of the amount of surface IgE), alterations in cytokine profiles (such as increase in type 1 cytokines *e.g.*, IL-2 and IFN-γ, vs. type 2 cytokines *e.g.*, IL-4, IL-5), alterations in Radio-Allergosorbent Test (RAST) results, or skin tests, as well as diminution or elimination of symptoms of an allergic response, such as urticaria, itching, malaise, anxiety, angioedema, constriction of the chest, nausea, vomiting, diarrhea, abdominal pain, dizziness, dyspnea, wheezing, stridor, dysphagia, dysarthria, hoarseness, weakness, confusion, fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis, mucus production, coughing, shock, stomach cramps, rhinitis, hay fever, asthma, inflammation, and the like.

Page 10, line 20, to page 11, line 2. Each of the exemplified allergic responses was well-known and well-documented in the art before the present specification was filed. Allergen immunotherapy, or injection of allergens for the purpose of modulating allergic responses, has been widely practiced for many years. See page 5, line 30, to page 7, line 2. See also Hellman *et al.*, *Handbook of Experimental Pharmacology 133*, 499-526, 1999.

Thus, according to the specification, intranodal delivery of an allergen accomplishes desensitization to allergens, as evidenced by modulation of the same well-known types of allergic responses that are modulated with conventional (*i.e.*, subcutaneous) allergen delivery; it does, however, make desensitization more efficient, less fraught with side effects, and more cost-effective.

The specification provides extensive teachings of common allergens to which desensitization often is desired. See page 1, line 20, to page 2, line 2; page 3, line 12, to page 4, line 21. Many more allergens, of course, were known in the art when the present specification was filed, as were formulations of the allergens for desensitization by subcutaneous injection. Methods of intranodal injection also were known in the art at the time of filing. *See, e.g.*, Hong *et al.*, *J. Immunol. Methods 120*, 151-57, 1989, Coupey *et al.*, *Cytokine 5*, 564-69, 1993 ("Coupey"), and WO 99/02183. The specification teaches that any such methods can be used: "The technique used for injection is within the skill of the art." Page 14, line 12. The specification also teaches that ultrasound, radiological, or other visualization means such as computerized axial tomography can be used to aid the injection. Page 13, line 29, to page 14, line 5. In addition, the specification teaches methods of formulating allergens for intranodal injection (page 12, line 12, to page 13, line 3) and dosage regimens (page 13, lines 4-28, and

Example 13). Finally, the specification provides working examples of allergen preparation (Examples 1-10), use of ultrasound to locate a lymph node (Example 11), intranodal allergen injection (Example 12), and numerous assays for detecting whether desensitization has occurred as a result of intranodal allergen injection (Example 14).

In spite of the clear teachings of the specification and the prior art, the U.S. Patent and Trademark Office appears to doubt that intranodal injection of allergens would work as described. But the Office Action has not provided a reasonable basis to question that intranodal injection of allergens would not work to desensitize an individual to the injected allergen. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993). To support a finding of non-enablement, the Office must not only explain why it doubts that intranodal injection of allergens would function as described, but also must support its assertions "with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. (BNA) 367, 370 (C.C.P.A. 1971). In this case, the Office has not provided acceptable evidence or reasoning that meets this standard.

The Office Action cites Guidry *et al.*, "Effect of Whole *Staphylococcus aureus* and Mode of Immunization on Bovine Opsonizing Antibodies to Capsule," *J. Dairy Sci. 77*, 2965-74, 1994 ("Guidry") as supporting its assertion that modulation of an allergic response by intranodal injection of any allergen but phospholipase A2 is unpredictable. Guidry is directed to immunization of cows against *S. aureus* infection. Guidry contains no teaching whatsoever that is relevant to desensitization of an individual to an allergen against which the individual mounts an allergic response, as recited in amended claim 1.

In any event, absolute predictability is not required for enablement. The standard for

whether a claim is enabled is whether any experimentation that must be carried out is undue. *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). However, this does not mean that no experimentation at all is permitted. Thus, even if routine experimentation were required to optimize the claimed methods, that does not make the experimentation undue:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 169 U.S.P.Q. 759 (2d. Cir. 1971), *cert. denied*, 404 U.S. 1018 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. In re Rainer, 52 CCPQ 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re Colianni, [561 F.2d 220, 195 US.P.Q. 150 (C.C.P.A. 1977)].

Ex parte Jackson, 217 U.S.P.Q. (BNA) 804, 807 (Bd. Pat. App. Interf. 1982).

Amended independent claim 1 recites a method of desensitizing an individual to an allergen comprising the step of delivering an allergen against which the individual mounts an allergic response directly into a lymph node of said individual. As noted above, successful desensitization against allergens by subcutaneous injection has been widely practiced for many years. Those of skill in the art expect to carry out routine testing of administration regimens to desensitize a particular individual to a particular allergen and would not find such routine testing to rise to the level of undue experimentation.

The Office merely speculates that intranodal injection of an allergen would not work to desensitize an individual against the allergen as taught in the specification. Speculation, however, should play no role in a determination of whether the present specification enables the

claimed methods. Guidry does not provide acceptable evidence to question the enablement provided in the specification or the vast teachings in the prior art that desensitization to allergens can be accomplished. The Office has cited no other evidence or acceptable reasoning to doubt the specification's extensive enabling teachings. Thus, a *prima facie* case of non-enablement has not been made. The rejection should be withdrawn.

Written Description

The Office Action also rejects claims 1-10, 14, 19-26, 45, and 46 as lacking sufficient written description. The purpose of the written description requirement of 35 U.S.C. § 112, first paragraph is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). What is required to satisfy the written description requirement depends on the nature of the invention claimed. *In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. (BNA) 592, 593 (C.C.P.A. 1971).

The Office Action asserts that the specification does not describe the generic method of claim 1, *i.e.*, "'modulating' *any* allergic response of an individual comprising the step of delivering *any* allergen, *any* extract or *any* purified substance, *any* recombinant protein and *any* synthesized peptide directly into a lymph node of said individual, whereby *any* allergic response is 'modulated.'" Page 5, fourth paragraph. Amended independent claim 1 is directed to a method of desensitizing an individual to an allergen. The claimed method involves intranodal delivery of an allergen against which the individual mounts an allergic response. The individual is thereby desensitized to the allergen. All that is required to satisfy the written description requirement for this subject matter is that the specification convey to those skilled in the art that

Applicants possessed this subject matter as of the filing date of the present application. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). *See also Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1327, 63 U.S.P.Q.2d (BNA) 1609, 1615 (Fed. Cir. July 15, 2002): "the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed." The present specification satisfies this requirement.

As noted above, use of allergen preparations – mainly by subcutaneous injection – to desensitize individuals against the allergens was well-known in the prior art. The novel aspect of the invention, *i.e.*, intranodal injection of allergens to desensitize an individual against an allergen to which the individual mounts an allergic response, is explicitly taught in the specification:

> The present invention involves the ***delivery of an allergen by injection directly into a lymph node*** in order to modulate an allergic response of an individual (for example, to elicit an IgG response) more efficiently than is possible by subcutaneous injection. According to the invention, modulation of an allergic response includes, but is not limited to, diminution or elimination of responses such as alterations in specific IgG levels, alterations in IgG ratios, alterations in specific IgE levels, ***lowered sensitivity to the allergen*** or to a cross-reactive allergenic agent, alterations in activated basophils (such as the reduction of the amount of surface IgE), alterations in cytokine profiles (such as increase in type 1 cytokines *e.g.*, IL-2 and IFN-γ, vs. type 2 cytokines *e.g.*, IL-4, IL-5), alterations in Radio-Allergosorbent Test (RAST) results, or skin tests, as well as diminution or elimination of symptoms of an allergic response, such as urticaria, itching, malaise, anxiety, angioedema, constriction of the chest, nausea, vomiting, diarrhea, abdominal pain, dizziness, dyspnea, wheezing, stridor, dysphagia, dysarthria, hoarseness, weakness, confusion, fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis, mucus production, coughing, shock, stomach cramps, rhinitis, hay fever, asthma, inflammation, and the like.

Page 10, line 17, to page 11, line 2, emphasis added. The specification also explicitly teaches that any substance that elicits an allergic response can be injected intranodally according to the claimed methods:

> An "allergen" according to the invention can be any substance or portion thereof that elicits an allergic response. For example, common allergens include bee venom, wasp venom, fire ant venom, pollens, including grass, tree and herb pollens, penicillin and other drugs, anesthetics, serum, animals, animal dander, cockroaches, dust mites, food allergens such as those found in peanuts, tree nuts, milk, fish, shellfish, eggs, soy, wheat, honey, fruits, viruses, bacteria, mold, protozoa, or latex. Allergens also can be any component of the allergen that elicits an allergic response, such as PLA2 in bee venom or urushiol in poison ivy. Likewise, an allergen can be a mixture of substances or a crude or purified extract of a generally allergenic composition. These allergens can be recovered from a natural source or can be a synthetic or non-naturally occurring substance, such as a recombinant protein, a synthesized peptide, or a mimetic chemical (including a peptide) that elicits an allergic response similar to a naturally occurring allergen.

Provided with these explicit teachings in the specification, as well as the extensive prior art teachings of common allergens and methods of desensitizing individuals to allergens by subcutaneous injection, one of skill in the art would recognize that Applicants were in possession of the generic method of claim 1 at the time the application was filed. Thus, the written description requirement is satisfied.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 19, 23, and 24 Under 35 U.S.C. § 112, second paragraph

Claims 19, 23, and 24 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse the rejection.

The Office Action notes that the recitation "administered" in claims 23 and 24 lacks antecedent basis in claim 1. Claims 23 and 24 have been amended to recited "delivered," which has antecedent basis in the recitation "delivering" in claim 1.

The Office Action asserts that the recitation "a delivery substance" in claim 19 is ambiguous and indefinite. To advance prosecution, claim 19 has been amended to delete "a delivery substance" and to recite instead "a physiologically acceptable carrier." The new recitation is supported at page 12, lines 19-20: "The allergen is preferably delivered in a physiologically acceptable carrier suitable for injection."

None of the amendments to claims 19, 23, and 24 add new matter or require a new search. Applicants respectfully request withdrawal of the rejection.

The Rejections Under 35 U.S.C. § 103(a)

The Office Action makes three rejections under 35 U.S.C. § 103(a):

- claims 1-5, 8, 9, 14, 19-26, 45, and 46 stand rejected under 35 U.S.C. § 103(a) as obvious over Hong *et al.*, *J. Immunol. Methods 120*, 151-57, 1989 ("Hong") in view of Hellman *et al.*, *Handbook of Experimental Pharmacology 133*, 499-526, 1999 ("Hellman"), Coupey *et al.*, *Cytokine 5*, 564-69, 1993 ("Coupey"), and Zinkernagel *et al.*, *Immunol. Rev. 156*, 199-209, 1997 ("Zinkernagel");

- claim 10 stands rejected under 35 U.S.C. § 103(a) as obvious over Hong in view of Hellman, Coupey, and Zinkernagel and further in view of Banks *et al.*, "Chemistry and Pharmacology of Honey-bee Venom," in VENOMS OF THE HYMENOPTERA, Piek, T., ed., 1986, pages 329-416 ("Banks"); and

- claims 6 and 7 stand rejected under 35 U.S.C. § 103(a) as obvious over Hong in view of Hellman, Coupey, and Zinkernagel and further in view of WO 99/02183.

Applicants respectfully traverse each of the rejections.

The U.S. Patent and Trademark Office must make three showings to establish a *prima facie* case that the methods of claims 1-10, 14, 19-26, 45, and 46 are obvious:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. The Office Action has not made a *prima facie* case that claims 1-10, 14, 19-26, 45, and 46 are obvious because there would have been no motivation for an ordinary artisan to have combined the cited references. Even if, *arguendo*, the teachings of the cited references were combined, the ordinary artisan would have had no reasonable expectation that intranodal injection of an allergen would successfully desensitize an individual to the allergen.

The rejection of claims 1-5, 8, 9, 14, 19-26, 45, and 46 over Hong in view of Hellman, Coupey, and Zinkernagel

Claims 1-5, 8, 9, 14, 19-26, 45, and 46 are directed to methods of desensitizing an individual to an allergen. The claimed methods involve intranodal delivery of an allergen against which the individual mounts an allergic response. The individual is thereby desensitized to the allergen.

Hong is cited as teaching modulation of an immune response (*i.e.*, production of monoclonal antibodies) after injection of human serum albumin into a lymph node of a mouse. Hellman is cited as teaching desensitization methods involving administration of allergens. Coupey is cited as teaching that injection of an antigen into the popliteal lymph node "prevent[s] tissue retention, catabolism, and dilution observed with subcutaneous or intravenous injections." Page 8, ¶ 8. Zinkernagel is cited as teaching that APCs bearing antigens must migrate to local lymph nodes to present antigens to T and B cells. The Office Action asserts that it would have been obvious to substitute Hellman's allergen in the method of Hong to deliver an antigen directly to APCs or immune cells within the lymph node.

The ordinary artisan, however, would not have been motivated to make the asserted combination. The primary reference, Hong, is directed to generation of monoclonal antibodies. Hong contains no teaching or suggestion at all that intranodal injection of an allergen could or should be used to desensitize an individual against the allergen. In fact, Hong contains no teaching at all regarding desensitization or allergic responses. Coupey, too, is directed to generation of antibodies and does not teach or suggest anything about desensitization to allergens. Zinkernagel does not address desensitization either. Although Hellman teaches desensitization methods, even the portion of Hellman that discusses alternative routes of allergen administration does not teach any alternative to subcutaneous injection except for oral

administration. See Section II, "Oral Administration of Recombinant Allergens or Allergen Extracts," on page 509. Nor does Hellman suggest that alternative routes of administration other than oral administration should be explored.

The Office Action asserts that the ordinary artisan would have been motivated to combine the cited references because (1) Hong teaches that strong primary immune responses occur after inguinal lymph node immunization, (2) Hellman teaches that injection of allergen to increase allergen-specific IgG can be effective for treating seasonal allergies, (3) Coupey teaches that intralymph node immunization enables direct triggering of the immune system, and (4) Zinkernagel teaches that APCs must migrate to the lymph nodes to present antigens to immune cells. Page 9, second full paragraph. The Office Action apparently equates increased IgG responses with effective desensitization. The asserted motivation is insufficient, however, because the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization.

For example, Bousquet *et al.*, 1988 (attached reference 1) demonstrated in a double-blind, placebo-controlled study with mixed grass-pollen allergoids that specific immunotherapy with allergoids reduced symptoms during the pollen season. The symptoms, however, were correlated with both nasal provocations with grass-pollen grains and the skin prick test but not with serum-specific IgG or IgE. The authors concluded in this study and other studies that IgG was <u>not</u> a predictor of a response for immunotherapy with grass-pollen allergoids. Djurup & Osterballe, 1984 (attached reference 2) examined the prognostic value of serum IgG subclass antibody levels undergoing grass pollen immunotherapy. Based on their results they concluded that a high IgG4 antibody response may in fact predict a <u>poor</u> clinical response to the treatment.

Numerous publications relating to venom immunotherapy (*e.g.*, Blaauw *et al.*, 1985 (attached reference 3) and Kampelmacher & van Der Zwan, 1987 (attached reference 4), reporting studies in which serum was taken immediately before hymenoptera sting challenge, suggest that specific IgG or IgG4 is of no predictive value in untreated patients, in patients on long term venom immunotherapy of more than three years' duration, or in patients in whom venom immunotherapy was stopped. Indeed, during the first 1-2 years of venom immunotherapy, the predictive value of serum antibodies is quite controversial: while Golden *et al.*, 1982 (attached reference 5) found an association with protection, others could not confirm this. See Ménardo *et al.*, 1988 (attached reference 6), Müller *et al.*, 1989 (attached reference 7), Thurnheer *et al.*, 1983 (attached reference 8), and Golden *et al.*, 1992 (attached reference 9). In a later study of Lawrence *et al.*, (attached reference 10), some of the patients with a "protective" IgG level reacted to the challenge, while most of those with specific IgG below this level did not.

In another study, Ewan *et al.*, 1993 (attached reference 11) investigated the correlation between venom-specific IgG antibodies in bee and wasp allergy. Ewan *et al.* showed that there was no correlation between the severity of the last systemic reaction and the venom IgG levels alone or venom IgG and IgE levels in analysis in either bee or wasp patients. These conclusions were also supported by the earlier studies of Keating *et al.*, 1991 (attached reference 12), which showed that venom skin test and venom specific antibody results do not predict the outcome of deliberate sting challenge or the sequent clinical course in individuals stopping VIT.

In summary, the ordinary artisan would have known that an increase in IgG levels is a poor predictor of clinical response after desensitization treatment. In fact, Hellman notes that the response observed with traditional methods of desensitization is not correlated with IgG

response observed with traditional methods of desensitization is not correlated with IgG concentrations: "However, improvement in symptoms is often correlated neither with increases in the concentration of antigen specific IgG nor with the decrease in the concentration of antigen specific IgE (Ohman 1992)." Page 507, first full paragraph. Thus, the ordinary artisan would not have reasonably expected that, merely because intranodal injection of antigens increases IgG levels, that intranodal injection of an allergen could be used successfully to desensitize a patient against the allergen, as recited in claims 1-5, 8, 9, 14, 19-26, 45, and 46. Thus, the ordinary artisan would not have been motivated to combine the teachings of Hong, Hellman, Coupey, and Zinkernagel. Even if, *arguendo*, these teachings were combined in the manner asserted in the Office Action, the ordinary artisan would not have reasonably expected that intranodal injection of an allergen could successfully desensitize an individual to that allergen.

The rejection of claim 10 over Hong in view of Hellman, Coupey, Zinkernagel, and Banks

Dependent claim 10 is directed to a method of desensitizing an individual against an allergen selected from the group consisting of allergenic components of bee venom, wasp venom, fire ant venom, pollen, mold, anesthetics, serum, drugs, animals, animal dander, cockroaches, dust mites, food allergens, poison ivy, poison oak, poison sumac, viruses, bacteria, protozoa, and latex. The species of bee venom has been searched. Hong, Hellman, Coupey, and Zinkernagel are applied as discussed above, and the Banks reference is cited as teaching administration of phospholipase A2, the primary allergen in bee venom, to build up the IgG levels in the serum of a subject to inhibit an allergic reaction against a bee sting. Office Action at page 10, fourth paragraph.

The arguments above with respect to Hong, Hellman, Coupey, and Zinkernagel apply with equal force to this rejection. The addition of Banks does not remedy the deficiencies of the

combination and supplies neither a motivation to combine the teachings of Hong, Hellman, Coupey, and Zinkernagel nor a reasonable expectation of success that intranodal injection of an allergen could desensitize an individual to that allergen. Again, a *prima facie* case of obviousness has not been made.

The rejection of claims 6 and 7 over Hong in view of Hellman, Coupey, Zinkernagel, and WO 99/02183

Dependent claim 6 recites use of an ultrasound device to monitor location of an injection needle in a method of desensitizing an individual against an allergen by delivering the allergen directly into a lymph node. Dependent claim 7 recites the step of visualizing the lymph node using a radiological method. Hong, Hellman, Coupey, and Zinkernagel are applied as discussed above, and WO 99/02183 is cited as teaching antigen delivery to the inguinal lymph node by inserting a catheter or needle under ultrasonographic control and as teaching use of radiography to image lymphatic flow to determine an insertion position. Page 11, paragraph 5.

The arguments above with respect to Hong, Hellman, Coupey, and Zinkernagel apply with equal force to this rejection. The addition of Banks does not remedy the deficiencies of the combination and supplies neither a motivation to combine the teachings of Hong, Hellman, Coupey, and Zinkernagel nor a reasonable expectation of success that intranodal injection of an allergen could desensitize an individual to that allergen. Again, a *prima facie* case of obviousness has not been made.

It is only the present specification that teaches that intranodal injection of an allergen can successfully desensitize an individual against the allergen. The U.S. Patent and Trademark Office has used Applicants' teachings as a template to select the elements of intranodal injection

and an allergen from the cited references and to combine them as the present specification teaches. Hindsight use of Applicants' specification, however, is not permitted.

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

In re Rouffet, 149 F.3d 1350, 1557, 47 U.S.P.Q.2d (BNA) 1453, 1457-58 (Fed. Cir. 1998).

Applicants respectfully request withdrawal of each of the three rejections under 35 U.S.C. § 103(a).

Respectfully submitted,

Dated: January 9, 2003

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Appendix 1.

Version of the amended claims and paragraphs, with markings to show changes made

CLAIMS

1. (amended) A method of [modulating an allergic response of] desensitizing an individual to an allergen comprising the step of delivering an allergen against which the individual mounts an allergic response directly into a lymph node of said individual, whereby the individual is desensitized to the allergen [allergic response modulated].

19. (amended) The method of claim 1 wherein the allergen further comprises a [delivery substance] physiologically acceptable carrier.

21. (amended) The method of claim 20 wherein the adjuvant is selected from the group consisting of alum, BCG, aluminum hydroxide, aluminum phosphate, calcium phosphate, a surface-active agent, a surface-active microparticle, a bacterial product, a chemokine, a cytokine, a hormone, chitosan, starch, alginate, a cellulose derivative, a protein, [water, a saline solution, a dextrose solution, albumin, or] and a nucleic acid.

23. (amended) The method of claim 1 wherein 1 to 5 doses of from about 0.01 μg to about 10 μg of the allergen are [administered] delivered.

24. (amended) The method of claim 1 wherein a dose of from about 0.1 μg to about 50 μg of the allergen is [administered] delivered.

SPECIFICATION

Page 13, line 4:

The allergen may be delivered in a dose of about 0.01 μg to about 10 μg or about 0.1 μg to 50 μg and more preferably in a dose from about 0.1 μg to about 10 μg, although the optimal dose may vary depending on the allergen being injected, the weight of the patient, the immune system of the patient, and the like. Effective treatment in many cases may be accomplished with one delivery. In some embodiments, treatment includes from 1 to 15 injections. In preferred embodiments, treatment includes from 1 to 5 injections and more preferably 1 to 3 injections. For example, the standard escalation after a test dose of 0.1 μg involves administration of 1 μg followed by 5 μg and 10 μg. Escalation depends on the patient's tolerance of the previous dose. Multiple injections may be delivered periodically, *e.g.*, over a course of days, once or twice per month, or several times per year.

The dose employed during the initial (desensitization) phase can be from about 0.01 μg to about 10 μg or 0.1 μg to 10 μg delivered in from 1 to 5, preferably from 1 to 3, injections of 1 μg, 5 μg and 10 μg over the course of from several days up to 3 months. In preferred embodiments, the allergen is delivered 2 to 3 times, 1 to 2 weeks apart. During desensitization treatment, 50 μl to 200 μl of an allergen-containing composition is administered directly into the lymph node starting with very small doses of allergen, from 0.1 μg up to 10 μg. This dose is one-tenth the normal dose for subcutaneous immunotherapy, and therefore the possibility of side effects is minimized.

The dose employed during the maintenance phase can be from about 0.01 μg to about 10 μg or 0.1 μg to 50 μg, preferably 0.1 μg to 20 μg, delivered periodically over the course of from

several months to several years. During maintenance treatment, the patient's lymph node is injected with from 0.1 μg to 50 μg of allergen in injections of typically 50 μl to 200 μl each. One skilled in the art will recognize that even smaller quantities of carrier are feasible.